AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (Currently amended) A method of performing targeted modifications of human embryonic stem (ES) cells, the method comprising the steps of

~~obtaining copies of a genetic construct, wherein the construct is a targeting vector comprising an insert flanked by 3' and 5' arms homologous to genomic regions flanking a site in the genome of the ES cells selected for insertion, so that homologous recombination will occur between the genetic construct and the selected regions of the stem cell genome~~;

electroporating ~~the~~ copies of ~~the~~ a genetic construct into clumps of human ES cells in a culture medium, wherein the construct comprises a marker gene for cellular identification on an insert flanked by 3' and 5' arms homologous to genomic regions that flank an insertion site in an ES cell genome, so that homologous recombination occurs between the 3' and 5' arms and the stem cell genomic regions; and

identifying cells ~~which~~ that contain the ~~genetic construct, wherein the construct includes~~ a marker gene ~~for cellular identification~~.

2. (Cancelled)

3. (Currently amended) A method as claimed in claim 1, wherein ~~there is no promoter on the marker gene in the genetic construct, the genetic construct being inserted into the ES cells in a location in the genome of the ES cells wherein~~ upon recombination, the marker gene is operably linked with a differentiation-specific promoter in the genome such that the marker gene is expressed only in cells in a desired state of differentiation.

4. (Currently amended) A method as claimed in claim 1 wherein the ~~vector~~ genetic construct includes a tissue-specific promoter ~~driving the~~ that drives expression of the marker gene ~~in the genetic construct, the tissue-specific promoter being~~ only in cells in a desired state of differentiation.

5. (Withdrawn) Human cells in culture derived from human embryonic stem cells, the cells comprising in their genome an inserted genetic construct which knocks out the functioning of a gene which would otherwise be expressed in those human cells in culture.

6. (Withdrawn) Human cells in culture derived from human embryonic stem cells, the cells comprising in their genome an inserted genetic construct which introduced a mutation into a native gene in those human cells in culture.

7. (Currently amended) A method of purifying cells of a defined lineage from a culture of human embryonic stem (ES) cells, the method comprising the steps of

~~(a) obtaining copies of a genetic construct, wherein the construct is a targeting vector comprising an insert flanked by 3' and 5' arms homologous to genomic regions flanking a site in the genome of the ES cells selected for insertion, so that homologous recombination will occur~~ between the genetic construct and the selected regions of the genome of the stem cells, the ~~genetic construct including a marker gene for cellular identification which will be expressed only in cells of the defined lineage~~;

~~(b)~~ (a) electroporating ~~the~~ copies of ~~the~~ a genetic construct into clumps of human ES cells in a culture medium, the genetic construct comprising an insert having a marker gene expressed only in the defined lineage cells, the insert flanked by 3' and 5' arms homologous to genomic regions that flank an insertion site in an ES cell genome so that homologous recombination occurs between the 3' and 5' arms and the stem cell genomic regions;

~~(c)~~ (b) identifying cells ~~which~~ that express the marker gene ~~from the genetic construct~~; and

~~(d)~~ (c) purifying the cells expressing the marker gene from cells not expressing the marker gene.

8. (Currently amended) A method as claimed in claim 7 wherein the marker gene ~~includes~~ is operably linked to a promoter ~~which is~~ active ~~to express a gene~~ only in the defined lineage cells ~~of the defined lineage~~.

9. (Original) A method as claimed in claim 7 wherein after the electroporating step, the ES cells are permitted to differentiate.

10. (Previously presented) A method as claimed in claim 7 wherein the marker gene encodes a fluorescent gene product and the identifying and purifying is performed by fluorescence activated cell sorting.

11. (Withdrawn) A culture of differentiated human cells derived from human ES cells and purified by the method of claim 7 for cells of a desired lineage.

12. (Previously presented) A method for purifying cells of a defined lineage obtained from human embryonic stem (ES) cells, the method comprising the steps of

a) identifying expressed genes characteristic of defined lineage cells purified by a method of Claim 7;

b) culturing non-transformed human ES cells under differentiating conditions to yield a culture that comprises differentiated cells; and

c) purifying defined lineage cells that express the characteristic genes from the culture that comprises differentiated cells.

13. (Previously presented) A method as claimed in claim 12 wherein the defined lineage is undifferentiated cells wherein the genes identified include genes for the cellular factors CD124, CD113, FGF-R, c-Kit, and BMP-4, and wherein the purifying step comprises the step of testing cells for expression of at least one gene selected from the group consisting of CD124, CD113, FGF-R, c-Kit, and BMP-4.

14. (Withdrawn) Human cells in culture derived from human embryonic stem cells, the cells comprising in their genome an inserted genetic construct which expresses an inserted gene only when the human cells are in a desired state of differentiation.

15. (Withdrawn) Human cells in culture as claimed in claim 14 wherein the desired state of differentiation is an undifferentiated state.

16. (Withdrawn) Human cells in culture as claimed in claim 14 where the gene is a marker gene the expression of which can be observed visually.

17. (Currently amended) A method of performing targeted modifications of human embryonic stem (ES) cells, the method comprising the steps of

a) electroporating copies of a genetic construct into clumps of human ES cells in a culture medium, wherein the construct ~~is a targeting vector comprising~~ comprises a foreign gene and a marker gene flanked by 3' and 5' arms homologous to genomic regions flanking an insertion site in ~~the~~ an ES cell genome ~~of the ES cells selected for insertion~~, so that homologous recombination ~~will~~ occurs between the ~~genetic construct~~ 3' and 5' arms and the ~~selected~~ stem cell genomic regions ~~of the stem cell genome~~,

(i) wherein the marker gene comprises a promoter active in cells of a defined lineage, or

(ii) wherein in the absence of a promoter, the construct is designed to recombine with the selected regions of the ES cell genome, such that the marker gene is operably linked to an endogenous, tissue specific promoter; and

b) identifying cells ~~which~~ that express the marker gene ~~from the genetic construct~~.

18. (Previously presented) The method of claim 17, further comprising purifying the cells of step b) expressing the marker from cells not expressing the marker, wherein the cells expressing the marker are of a defined lineage.

19. (Previously presented) The method of claim 1, wherein copies of the genetic construct are electroporated into human ES cells with a single 320 volt, 200 microfarad pulse.

20. (Previously presented) The method of claim 7, wherein copies of the genetic construct are electroporated into human ES cells with a single 320 volt, 200 microfarad pulse.

21. (Previously presented) The method of claim 17, wherein copies of the genetic construct are electroporated into human ES cells with a single 320 volt, 200 microfarad pulse.